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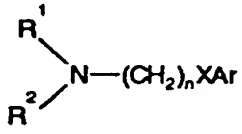
(54) Title: HETEROCYCLIC AMINES FOR TREATING ISCHAEMIC STROKES

(57) Abstract

Use of compounds of formula (I), wherein R^1 and R^2 each independently represent: hydrogen, C_{1-8}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-4}alkyl, arylC_{1-4}alkyl, C_{2-6}hydroxyalkyl or $R^3R^4NC_{2-6}$alkyl (where R^3 and R^4 independently represent H or C_{1-4}alkyl) or NR^1R^2 represents a saturated heterocyclic ring containing 4 to 9 ring members, one of which may optionally be a further heteroatom selected from O, S or NR^5 (where R^5 is H, C_{1-4}alkyl or arylC_{1-4}alkyl), which ring may optionally be substituted by one or two substituents selected from C_{1-6}alkyl and C_{1-6}alkoxy; X represents O, S, or C=O; n is 5 to 11; and Ar represents phenyl optionally substituted by 1-3 substituents selected from halo, C_{1-8}alkyl, C_{1-8}alkoxy, C_{1-2}alkylenedioxy, e.g. methylenedioxy, trifluoromethyl, trifluoromethyloxy, or by a group $Ph(Alk^1)_pA(Alk^2)_q$- where Ph is optionally substituted phenyl, A is a bond, O, S, -C=O or CH=CH, Alk^1 and Alk^2 independently represent C_{1-4}alkyl which may be straight or branched and p and q are independently 0 or 1 provided that the length of -$(Alk^1)_pA(Alk^2)_q$- does not exceed 5 atoms, or Ar is an optionally substituted tricyclic heteroaryl group (a), in which Y^1 is $Y^2(CH_2)_r$ where r is 0 or 1 and Y^2 is O, S or NR^6 where R^6 is hydrogen or C_{1-4}alkyl, Z is $(CH_2)_s$ or -CH=CH-, s is 0, 1 or 2 or Ar is the corresponding tricyclic dehydro ring system; with the provisos that (i) when X is O or S, and NR^1R^2 represents a heterocyclic ring which does not contain an optional further heteroatom then Ar is phenyl substituted by a group $Ph(Alk^1)_pC(O)(Alk^2)_q$-; (ii) when n is 5 and one of R^1 and R^2 is hydrogen, C_{1-4}alkyl or arylC_{1-4}alkyl, then the other of R^1 and R^2 is not $R^3R^4NC_{2-6}$alkyl; and pharmaceutically acceptable salts thereof; in the manufacture of a medicament for the treatment of a condition where a calcium antagonist is required. Certain novel compounds of formula (I) and processes for preparing them are also described.



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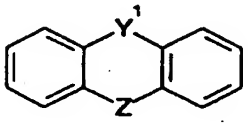

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HETEROCYCLIC AMINES FOR TREATING ISCHAEMIC STROKES

The present invention relates to amine derivatives, more particularly aryloxy-, arylthio- or aroyl-alkylamino compounds, to processes for their preparation, pharmaceutical compositions containing them and their use in therapy, in particular in the treatment of ischaemic stroke.

Stroke is reportedly the third most common cause of death in the developed world. Current therapies for ischaemic stroke are limited and have a number of disadvantages, such as the risk of exacerbating haemorrhage. There is therefore a need for new and improved treatments for ischaemic stroke.

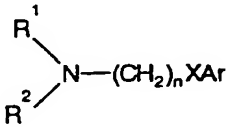
EP-A-103252 discloses a broad class of aryloxyalkylamino derivatives. These compounds are said to have utility as herbicides.

French Patent Application No. 1601591 describes a class of nitrogen-containing heterocyclic compounds derived from phenoxyalkyl alcohols, which are said to be cholesterol-lowering agents.

British Patent No. 924961 describes, as intermediates for the preparation of anti-nematodal agents, compounds of formula R.W.CH_2.CH_2.NXY, wherein R is phenyl optionally substituted by *inter alia* halogen, alkyl or alkoxy, X and Y are *inter alia* alkyl, or NXY represents a pyrrolidino, piperidino or morpholino group and W is a straight saturated chain containing up to 16 carbon atoms and 1 to 3 non-adjacent oxygen atoms.

We have now found that certain amine derivatives exhibit activity as calcium channel antagonists.

The present invention therefore provides, in a first aspect, the use of a compound of formula (I):



Formula (I)

wherein

R^1 and R^2 each independently represent:

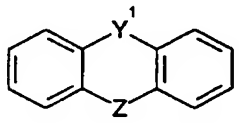
hydrogen, C_{1-8}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-4}alkyl, arylC_{1-4}alkyl, C_{2-6}hydroxyalkyl or $R^3R^4NC_{2-6}$alkyl (where R^3 and R^4 independently represent H or C_{1-4}alkyl) or

NR^1R^2 represents a saturated heterocyclic ring containing 4 to 9 ring members, one of which may optionally be a further heteroatom selected from O, S or NR^5, (where R^5 is H, C_{1-4}alkyl or arylC_{1-4}alkyl), which ring may optionally be substituted by one or two substituents selected from C_{1-6}alkyl and C_{1-6}alkoxy;

X represents O, S, or C=O;

n is 5 to 11; and

Ar represents phenyl optionally substituted by 1-3 substituents selected from halo, C_{1-8}alkyl, C_{1-8}alkoxy, C_{1-2}alkylenedioxy e.g. methylenedioxy, trifluoromethyl, trifluoromethyloxy, or by a group $Ph(Alk^1)_pA(Alk^2)_q$- where Ph is optionally substituted phenyl, A is a bond, O, S, -C=O or CH=CH, Alk^1 and Alk^2 independently represent C_{1-4}alkyl which may be straight or branched and p and q are independently 0 or 1 , provided that the length of $(Alk^1)A(Alk^2)$ does not exceed 5 atoms, or Ar is an optionally substituted tricyclic heteroaryl group:



in which Y^1 is $Y^2(CH_2)_r$ where r is 0 or 1 and Y^2 is O, S or NR^6 where R^6 is hydrogen or C_{1-4}alkyl, Z is $(CH_2)_s$ or -CH=CH-, s is 0, 1 or 2 or Ar is the corresponding tricyclic dehydro ring system;

with the provisos that

(i) when X is O or S, and NR^1R^2 represents a heterocyclic ring which does not contain an optional further heteroatom then Ar is phenyl substituted by a group $Ph(Alk^1)_pC(O)(Alk^2)_q$-

(ii) when n is 5 and one of R^1 and R^2 is hydrogen, C_{1-4}alkyl or arylC_{1-4}alkyl, then the other of R^1 and R^2 is not $R^3R^4NC_{2-6}$alkyl;

or a pharmaceutically acceptable salt thereof; in the manufacture of a medicament for the treatment of conditions where a calcium antagonist is required.

Compounds of formula (I) and their pharmaceutically acceptable salts are preferably used in the manufacture of a medicament for the treatment of conditions related to the accumulation of calcium in the brain cells of mammals.

In compounds of formula (I), n is preferably from 5 to 9, most preferably 7.

X preferably represents oxygen or C=O.

When Ar is substituted by a group $Ph(Alk^1)_pA(Alk^2)q$-, A is preferably oxygen, C=O or a bond. Alk^1 and Alk^2 preferably independently represent CH_2 or when branched, $C(H)(CH_3)$ or $C(CH_3)_2$. When A is oxygen q is preferably zero and p is preferably zero or 1. When A is a bond the sum of p + q is preferably 1 or 2. When A represents CH=CH or C=O, p and q are preferably both zero.

Examples of tricyclic heteroaryl groups Ar include dibenzofuranyl, dibenzothienyl, carbazole, N-methylcarbazole, acridine and dibenzoxepine. The tricyclic moiety can be linked to the remainder of formula (I) via any suitable ring atom.

Suitable substituents for Ph, and tricyclic heteroaryl groups include, for example, 1 to 3 substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl and C_{1-4}alkoxy.

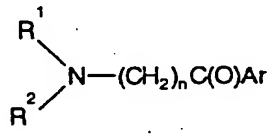
Preferably Ar is phenyl mono-substituted by a halogen atom or by a group selected from phenoxy, benzoyl, halobenzoyl or benzyl or benzyloxy in which the $-CH_2-$ moiety may optionally be substituted by one or two methyl groups; or Ar is phenyl disubstituted by a halogen atom; or Ar is 2-dibenzofuranyl. Most preferably Ar is phenyl substituted by benzyl, benzoyl, fluorobenzoyl, chlorobenzoyl or benzyloxy. The substituent is preferably at the 3- or 4- position of the phenyl ring.

Alkyl groups present in the compounds of formula (I), alone or as part of another group, can be straight or branched. Thus, a C_{1-6}alkyl group may be for example methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl or any branched isomer thereof such as isopropyl, t-butyl, or sec-pentyl.

It will be appreciated that for use in medicine a salt of a compound (I) should be pharmaceutically acceptable. Examples of pharmaceutically acceptable salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, methanesulphonate or similar pharmaceutically acceptable inorganic or organic acid addition salts. Other non-pharmaceutically acceptable salts may be used for example in the isolation of a final product and are included within the scope of this invention.

It will be appreciated that the compounds of formula (I) may contain one or more asymmetric centres. Such compounds will exist as optical isomers (enantiomers). Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixtures of the two are included within the scope of the invention. Further, all diastereomeric forms possible (pure enantiomers and mixtures thereof) are within the scope of the invention.

Certain compounds of formula (I) are believed to be novel. Thus, in a further aspect the invention provides novel compounds of formula (IA):

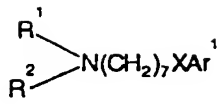


Formula (IA)

wherein

R^1, R^2, n and Ar are as defined for formula (I); and salts thereof.

In a yet further aspect the invention also provides a compound of formula (IB) :



Formula (IB)

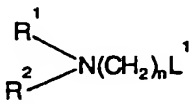
and salts thereof, wherein R^1, R^2, and X are as defined for formula (I) and Ar^1 represents phenyl optionally substituted by a group $Ph(Alk^1)_pA(Alk^2)q$- or a tricyclic heteroaryl group as defined for formula (I), provided that when X is O or S, and NR^1R^2 represents a heterocyclic ring which does not contain an optional further heteroatom then Ar^1 is phenyl substituted by a group $Ph(Alk^1)_pC(O)(Alk^2)_q$-.

Particular compounds of the invention, which are believed to be novel compounds include:

N-[7-(4-benzyloxyphenoxy)heptyl]-N-methylcyclohexylamine,
N-[7-(4-benzyloxyphenoxy)heptyl]methylamine,
N-[7-(4-benzyloxyphenoxy)heptyl]dimethylamine,
N-[7-(4-benzyloxyphenoxy)heptyl]-N-methyl-N',N'-dimethylethylenediamine,
N-[7-(4-benzyloxyphenoxy)heptyl]-N-butylmethylamine,
N-[7-(4-benzyloxyphenoxy)heptyl]morpholine,
N-[7-(4-benzyloxyphenoxy)heptyl]cyclohexylamine,
1-[7-(4-benzyloxyphenoxy)heptyl]-4-methylpiperazine,
1-[7-(4-benzoylphenoxy)heptyl]piperidine,
1-[7-(3-benzoylphenoxy)heptyl]piperidine,
1-{7-[4-(4-fluorobenzoyl)phenoxy]heptyl}piperidine,
1-{7-[4-(1-Methyl-1-phenylethyl)phenoxy]heptyl}piperidine,
1-{7-[4-(4-chlorobenzoyl)phenoxy]heptyl}piperidine,
(±)-1-{7-[4-(1-phenylethyloxy]phenoxy]heptyl}piperidine,
6-[4-(4-fluorophenoxy)phenyl]-6-oxo-1-piperidinylhexane,
8-[4-(4-fluorophenoxy)phenyl]-8-oxo-1-piperidinyloctane,
6-(4-phenoxy)phenyl-6-oxo-1-piperidinylhexane,
and salts thereof.

The compounds of the present invention can be prepared by processes analogous to those known in the art. The present invention therefore provides in a further aspect, a process for the preparation of a novel compound of formula (I) which comprises:

(a) to prepare a compound wherein X represents O or S reaction of a compound of formula (II):



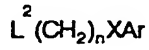
Formula (II)

in which R^1, R^2, and n are as defined in formula (I), and L^1 is a group displaceable with a nucleophile with a compound of formula (III) :

Formula (III)

in which Ar and X are as defined in formula (I);

(b) reaction of a compound of formula (IV) :



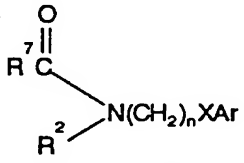
Formula (IV)

in which Ar, X and n are as defined for formula (I),and L^2 is a leaving group, with a compound of formula (V) :

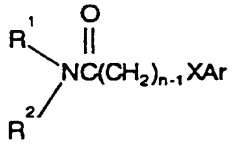
Formula (V)

in which R^1 and R^2 are as defined in formula (I); or

(c) reduction of an amide of formula (VI) or (VII) :



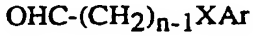
Formula (VI)



Formula (VII)

wherein R^1, R^2, X, Ar and n are as defined above and  is a group reducible to R^1;

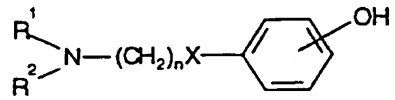
d) Reductive amination of an aldehyde of formula (VIII) :



Formula (VIII)

wherein Ar, X, and n are as hereinbefore defined, in the presence of a compound of formula (V) as defined above.

e) To prepare a compound wherein Ar represents phenyl substituted by $Ph(Alk^1)_pO$-, alkylation of a compound of formula (IX) :



Formula (IX)

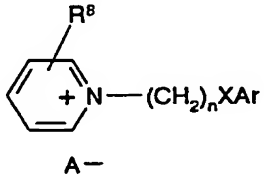
wherein R^1, R^2, X, and n are as hereinbefore defined; with an alkylating agent of formula (X) :

$$Ph(Alk^1)_pL^1$$

Formula (X)

wherein Ph, Alk^1, p and L^1 are as hereinbefore defined.

f) To prepare a compound where R^1R^2N- represents an optionally substituted piperidine ring, reduction of a pyridine derivative of formula (XI) :



Formula (XI)

wherein Ar, X, and n are as hereinbefore defined, R^8 represents hydrogen or an optional substituent as hereinbefore defined and A^- is a counter anion;

g) to prepare a compound where X represents O or S, reaction of a compound of formula (XII) :

$$R^1R^2N(CH_2)_nXH$$

Formula (XII)

wherein R^1, R^2 and n are as hereinbefore defined and X is O or S,
with a compound F-Ar;

h) Interconversion of one compound of formula (I) to a different compound of formula (I) e.g.

(i) reduction of a compound wherein A represents CH=CH to a compound wherein A represents $-CH_2CH_2-$;

(ii) reduction of a compound wherein A and/or X represent C=O to a compound wherein A and/or X represent $-CH_2-$;

followed if desired by salt formation.

In process (a) the reaction between a compound of formula (II) and a compound of formula (III) can be carried out under standard conditions. For example when L^1 is hydroxy, the reaction is carried out in the presence of diethyl azodicarboxylate and triphenyl phosphine. Such a reaction is known as the Mitsunobu reaction (as described in Synthesis 1981, 1). This reaction may optionally be effected in the presence of a solvent such as tetrahydrofuran. Alternatively the leaving group L^1 may be for example a halogen atom or a sulphonyloxy group eg. methane-sulphonyloxy or p-toluene sulphonyloxy. In this case the reaction may be effected in the absence or presence of solvent such as dimethylformamide or methylethylketone in the presence of a base such as sodium hydride or potassium carbonate and at a temperature in the range 0 to 200°C.

The reaction of a compound of formula (IV) with a compound of formula (V) according to process (b) may be effected in conventional manner, for example using excess amine as solvent or alternatively using an organic solvent, e.g. an alcohol such as methanol or ethanol; dimethylformamide, or chloroform. The leaving group L^2 may be for example a halide such as bromide or chloride, an acyloxy group such as acetoxy or chloroacetoxy or a sulphonyloxy group such as methanesulphonyloxy or p-toluenesulphonyloxy. The reaction may be carried out in the presence of a base such as potassium carbonate, sodium hydride or potassium t-butoxide or an excess of the amine (V) may be employed.

Reduction of an amide of formula (VI) or (VII) according to process (c) may be effected using a suitable reducing agent such as lithium aluminium hydride. It will be appreciated that in this case X or A should not represent C=O unless simultaneous reduction of X and/or A is desired.

In process (d) reductive amination of an aldehyde (VIII) may be effected using a reducing agent such as sodium cyanoborohydride in the presence of a compound of formula (V), according to procedures well known in the art.

In process (e) the reaction of compounds (IX) and (X) may be effected in an analogous manner to process (a) described above.

Reduction of a pyridinium derivative (XI) according to process (f) may be effected for example by hydrogenation, using a noble metal catalyst such as palladium on charcoal, platinum or platinum oxide (Adam's catalyst), suitably in a solvent such as an alcohol e.g. ethanol.

In process (g) the reaction between a compound of formula (XII) and a compound F-Ar is preferably effected in the presence of a strong base such as sodium hydride, and in a polar organic solvent such as dimethylsulphoxide or dimethylformamide.

Interconversion reactions according to process (h) may be carried out using standard methods. Thus for example conversion of a compound (I) wherein A represents -CH=CH- into a compound (I) wherein A represents $-CH_2CH_2-$ may be effected by

catalytic hydrogenation and reduction of a compound where X and/or A represents C=O may be effected using a suitable reducing agent such as lithium aluminium hydride.

A compound of formula (II) can be prepared under standard alkylation conditions by reacting a compound of formula (XIII) :

$$L^2\text{-}(CH_2)_nL^1$$

Formula (XIII)

in which L^1, L^2 and n are as hereinbefore defined, with a compound of formula (V) as hereinbefore defined. The reaction is suitably carried out under analogous conditions to those described above for process (b).

It will be appreciated that in compounds of formula (XIII) the leaving groups L^1 and L^2 are preferably selected so that the compound of formula (V) reacts selectively with L^2. For example, in a compound of formula (XIII) L^1 is suitably hydroxy and L^2 is suitably halo.

Compounds of formula (III) are commercially available or may be prepared using standard procedures well known in the art.

Compounds of formula (IV) can be prepared by reacting a compound of formula (III) as hereinbefore defined with a compound of formula (XIII) as hereinbefore defined. In this reaction both L^1 and L^2 can be identical, for example halo. The reaction is suitably carried out in the presence of a weak base such as potassium carbonate. Alternatively the reaction may be carried out under phase transfer conditions using a strong base such as potassium hydroxide. Alternatively where X represents C=O a compound of formula (IV) may be prepared by Friedel-Craft acylation of a compound HAr with an acylating agent of the formula $L^2(CH_2)_nC(O)Hal$, where Hal represents a halogen atom such as bromo or chloro. The carbonyl group in the resulting compound of formula (IV) may if desired subsequently be reduced.

Compounds of formula (V) and (XIII) are commercially available or may be prepared by standard methods.

Compounds of formula (VI) may be prepared according to general processes (a) and (b) described herein employing an appropriate amide corresponding to formula (II) or (V).

Compounds of formula (VII) may be prepared by acylation of a compound of formula (V) for example with an appropriate acid chloride or ester, which may itself be prepared from a compound of formula (III) by reaction with an appropriate, commercially available bromoalkyl ester or acid, followed if necessary or desired by conversion to an acid chloride. Alternatively a compound (VII) may be prepared by a method analogous to process (a).

An aldehyde of formula (VIII) may be prepared for example by reduction of the corresponding nitrile using a reducing agent such as diisobutyl aluminium hydride, in the presence of an inert solvent such as toluene. Conveniently reductive amination of the aldehyde is carried out *in situ*, i.e. the compound of formula (I) is obtained from the nitrile in a one-pot reaction without isolation of the intermediate aldehyde. The nitrile may itself be prepared by reacting a compound of formula (IV) wherein L^2 is halo with potassium cyanide. Compounds (VIII) may also be prepared by other standard procedures such as reduction of an ester or oxidation of an alcohol.

Compounds of formula (IX) may be prepared by methods analogous to any of processes (a) - (d) described herein. Alternatively a compound (IX) may be obtained by catalytic hydrogenation of a corresponding compound of formula (I) wherein Ar represents a benzyloxyphenyl group. This therefore provides a further method of converting a compound of formula (I) to a different compound of formula (I).

Compounds of formula (X) are commercially available or are known in the literature.

Compounds of formula (XI) may be prepared in a similar manner to process (b) described above, employing a substituted pyridine as the amine.

Compounds of formula (XII) may be prepared as described for compounds of formula (II).

It will be appreciated that during certain of the above processes (a) to (h) as well as during the preparation of intermediates it may be necessary to protect any unsubstituted nitrogen atoms present in the molecule, with for example an N-protecting group, which may subsequently removed by methods well known in the art. Suitable protecting groups include aralkyl groups such as benzyl, diphenylmethyl or triphenylmethyl and acyl groups such as acetyl, trifluoroacetyl, benzoyl, methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl or benzyloxycarbonyl. An aralkyl group such as benzyl may be cleaved by hydrogenolysis, and an acyl group such as benzoyl may be cleaved by hydrolysis.

When a compound of formula (I) is obtained as a mixture of enantiomers, these may be separated by conventional methods such as crystallisation in the presence of a resolving agent, or chromatography, for example using a chiral HPLC column.

The invention also encompasses any novel intermediates described herein, in particular those of formulae (II), (IV), (VI), (VII), (IX) and (XI).

Compounds of the invention have been found to exhibit high calcium influx blocking activity, for example in neurons. As such the compounds are expected to be of use in therapy in treating conditions and diseases related to an accumulation of calcium in the brain cells of mammals, in particular humans. For example, the compounds are expected to be of use in the treatment of anoxia, ischaemia including for example stroke, migraine, visceral pain, epilepsy, traumatic head or spinal injury, AIDS-related dementia,

neurodegenerative diseases such as Alzheimer's disease and age-related memory disorders, mood disorders and drug addiction withdrawal such as ethanol addiction withdrawal.

The invention also provides a method of treatment of conditions or diseases related to (e.g. caused or exacerbated by) the accumulation of calcium in the brain cells of mammals which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) as hereinbefore defined or a pharmaceutically acceptable salt thereof.

Thus for example, the present invention provides a method of treatment of anoxia, ischaemia including for example stroke, migraine, visceral pain, epilepsy, traumatic head or spinal injury, AIDS-related dementia, neurodegenerative diseases such as Alzheimer's disease and age-related memory disorders, mood disorders and drug addiction withdrawal such as ethanol addiction withdrawal, which comprises administering to a subject in need thereof, an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

For use in medicine, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a novel compound of formula (I) as hereinbefore defined or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

The compounds of the invention may be administered by any convenient method for example by oral, parenteral, buccal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly. Parenteral administration is generally preferred.

The compounds of formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for

example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Compounds of the invention may also be administered parenterally, by bolus injection or continuous infusion. Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Both liquid and solid compositions may contain other excipients known in the pharmaceutical art, such as cyclodextrins.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 60 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 500 mg, preferably between 1 mg and 250 mg, eg. 5 to 200 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 60 mg, eg. 1 to 40 mg of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Alternatively the compounds of the invention may be administered by continuous intravenous infusion, preferably at a dose of up to 400 mg per day. Thus the total daily dosage by oral administration could be in the range 1 to 2000 mg and the total daily dosage by parenteral administration could be in the range 0.1 to 400 mg. The compounds may be administered for a period of continuous therapy, for example for a week or more.

If desired a compound of formula (I) or a pharmaceutically acceptable salt thereof may be administered in combination or concurrently with one or more other therapeutic agents, for example a thrombolytic agent such as anistreplase, streptokinase or a tissue plasminogen activator; an excitatory amino acid antagonist such as an NMDA antagonists; a free radical inhibitor; or a calpain inhibitor.

BIOLOGICAL DATA

In Vitro

Ca^{2+} Current Measurement

Cell preparations

Sensory neurons from dorsal root ganglia were dissociated from 1 day old rat pups (Forda et al, Developmental Brain Research, 22 (1985), 55-65). Cells were plated out onto glass coverslips and used within 3 days to permit effective voltage clamp of Ca^{2+} currents. Superior cervical ganglion neurons were isolated and cultured following a method modified from Marrion et al, Neurosci. Lett., 77, 55-60 (1987). Cells were plated onto laminin coated plastic tissue culture dishes and incubated at 37°C until just prior to recording. Electrophysiological recordings were performed from 2 to 9 days after dissociation.

Solutions

The pipette (internal solution) contained in mM: CsCl, 130; HEPES, 10; EGTA, 10; $MgCl_2$, 4; ATP, 2; buffered to pH 7.2 with CsOH. Cells were bathed in a normal Tyrodes solution before establishment of whole cell recording when the bathing solution was changed to one allowing isolation of Ca^{2+} currents. The external solution for recording Ca^{2+} channel currents contained in mM: $BaCl_2$, 10; TEA-Cl, 130; glucose, 10; HEPES, 10; $MgCl_2$, 1; buffered to pH 7.3 with TEA-OH. Barium was used as the charge carrier as this assists in current isolation and calcium dependent inactivation of current is avoided. Compounds were dissolved in DMSO to make a 20 mM stock solution. At the drug concentration used the vehicle (0.1%) had no significant effect on Ca^{2+} currents. All experiments were performed at 21 to 24°C. Whole cell currents were recorded using List EPC-7 amplifiers and stored, digitised for later analysis using PC based software similar to that described previously (Benham & Tsien, Journal of Physiology (1988), **404**, 767-784).

Ca^{2+} currents

Peak voltage gated Ca^{2+} channel currents of up to 10 nA from dorsal root ganglion neurons were recorded using 10 mM Ba^{2+} as charge carrier. Currents were evoked from a holding potential of -80 mV to a test potential of 0 or +10 mV every 15 seconds. This test potential was at the peak of the current voltage relationship and assessing block at this point reduced any errors due to drifting holding potential. Some cells showed slow rundown of current as is commonly seen when recording Ca^{2+} currents. The rundown rate was measured in control conditions and extrapolated through the time of drug application to derive a rundown corrected control value.

Dorsal Root Ganglion Cells

Block by 20 μM drug was assessed 3 minutes after drug application.

In this test compounds of Examples 1 to 10 gave percentage inhibition of plateau Ca^{2+} current in the range 62-99%.

Superior Cervical Ganglion Cells

Once a constant calcium current had been recorded for 4 successive pulses (1 minute) 10 μM Nimodipine, a dihydropyridine, was applied to the cell to block L type calcium current. After three minutes 5μM drug was coapplied with 10μM Nimodipine for three minutes. Such drug application tested the block of the remaining, predominantly N type, calcium current.

In this test compounds of Examples 9 to 15 gave percentage inhibition of plateau Ca^{2+} current in the range 70 to 96%.

Pharmaceutical Formulations

The following represent typical pharmaceutical formulations according to the present invention, which may be prepared using standard methods.

IV Infusion

Compound of formula (I)	1-40 mg
Buffer	to pH ca 7
Solvent/complexing	to 100 ml

Bolus Injection

Compound of formula (I)	1-40 mg
Buffer	to pH ca 7
Co-Solvent	to 5 ml

Buffer : Suitable buffers include citrate, phosphate, sodium hydroxide/hydrochloric acid.

Solvent : Typically water but may also include cyclodextrins (1-100 mg) and co-solvents such as propylene glycol, polyethylene glycol and alcohol.

Tablet

Compound	1 - 40 mg
Diluent/Filler *	50 - 250 mg
Binder	5 - 25 mg
Disentegrant *	5 - 50 mg
Lubricant	1 - 5 mg
Cyclodextrin	1 - 100 mg

* may also include cyclodextrins

Diluent : e.g. Microcrystalline cellulose, lactose, starch

Binder : e.g. Polyvinylpyrrolidone, hydroxypropymethylcellulose

Disintegrant : e.g. Sodium starch glycollate, crospovidone

Lubricant : e.g. Magnesium stearate, sodium stearyl fumarate.

Oral Suspension

Compound	1 - 40 mg
Suspending Agent	0.1 - 10 mg
Diluent	20 - 60 mg
Preservative	0.01 - 1.0 mg
Buffer	to pH ca 5 - 8
Co-solvent	0 - 40 mg
Flavour	0.01 - 1.0 mg
Colourant	0.001 - 0.1 mg

Suspending agent : e.g. Xanthan gum, microcrystalline cellulose
Diluent : e.g. sorbitol solution, typically water
Preservative : e.g. sodium benzoate
Buffer : e.g. citrate
Co-solvent : e.g. alcohol, propylene glycol, polyethylene glycol, cyclodextrin

The invention is further illustrated by the following non-limiting examples:

Intermediate 1

7-(4-Benzyloxyphenoxy)-1-bromoheptane

1,7-Dibromoheptane (12.9g) was added dropwise to a stirred solution of 4-benzyloxyphenol (10g), sodium hydroxide (2.5g), benzyltriethylammonium chloride (0.4g) and water (30ml). The mixture was stirred at 50°C for 18 hours, water (50ml) added and the solution extracted with dichloromethane (2 x 100ml). The combined dichloromethane extracts were dried over magnesium sulphate, solvent was removed and the residue was chromatographed on silica gel eluted with hexane/dichloromethane to give the **title compound** (4.25g) as a solid. m.p. 56 - 59°C.

Intermediate 2

7-Piperidinoheptanol

7-Bromoheptanol (5.0g) was added over 30 minutes to piperidine (20ml) stirred at room temperature. The resulting mixture was left to stand for 60 hours and then dissolved in chloroform. This solution was washed with dilute sodium hydroxide solution, brine containing a few drops of dilute sodium hydroxide solution and dried over magnesium sulphate. The solvent was removed and the residue was Kugelrohr distilled to give the **title compound** as a solid (4.53g) m.p. 37-39°C.

Intermediate 3

1-Bromo-6-[4-(4-fluorophenoxy)phenyl]-6-oxyhexane

A mixture of aluminium chloride (4.0g) in dry dichloromethane under an atmosphere of argon was treated with 6-bromohexanoyl chloride (6.4ml). The resulting solution was stirred for 20 minutes then added to a solution of 4-fluorodiphenylether (5g) in dichloromethane (100ml). The addition took 20 minutes and the mixture was stirred for a further 18 hours. The mixture was treated with water and the organic phase was separated, washed with dilute sodium hydroxide solution and brine, dried over sodium sulphate and the solvent removed. Recrystallisation from ethyl acetate-hexane gave the **title compound** as a white solid, (6.04g), m.p. 85 - 87°C.

Found: C, 59.02; H, 5.03%
($C_{18}H_{18}BrFO_2$) requires: C, 59.19; H, 4.97%

Intermediate 4

1-Bromo-8-[4-(4-fluorophenoxy)phenyl]-8-oxyoctane

Using similar conditions to the preparation of Intermediate 3 starting from 8-bromooctanyl chloride (7.24g) and using corresponding molar amounts of the other reagents gave the **title compound** as an oil (11.06g) which was used without further purification.

Intermediate 5

1-Bromo-6-(4-phenoxy)phenyl-6-oxyhexane

Using the conditions used to prepare Intermediate 3 starting from 6-bromooctanoyl chloride (20g) and using corresponding molar amounts of the other reagents gave the **title compound** as an oil which was used without further purification.

Example 1

N-[7-(4-Benzyloxyphenoxy)heptyl]-N-methylcyclohexylamine hydrochloride

A mixture of 7-(4-benzyloxyphenoxy)-1-bromoheptane (1.88g), 80% sodium hydride (0.17g) and dimethylformamide (10ml) was stirred under nitrogen for 5 minutes. N-methylcyclohexylamine (0.65ml) was added by syringe and the mixture was stirred at 60°C for 4 hours. The solvent was removed and the residue treated with water and extracted with ether. The ether layer was separated, treated with dilute hydrochloric acid and the resulting solid was collected, chromatographed on silica gel eluted with dichloromethane-methanol and recrystallised from ethyl acetate to give the **title compound**, (0.674g) m.p. 107 - 108°C.
Found: C, 72.37; H, 8.86; N, 3.40 ; Cl, 7.78%
($C_{27}H_{39}NO_2$.HCl) requires: C, 72.70; H, 9.04; N, 3.14; Cl, 7.95%

Example 2

N-[7-(4-Benzyloxyphenoxy)heptyl]methylamine hydrochloride

A solution of 7-(4-benzyloxyphenoxy)-1-bromoheptane (1.25g) in chloroform (20ml) methanol (10ml) and ethanol (10ml) was treated with 8M methylamine in ethanol (20ml). The solution was allowed to stand at room temperature for 60 hours, the solvent was removed and the residue dissolved in chloroform. This solution was washed with dilute sodium hydroxide solution and brine, dried over sodium sulphate and the solvent was removed. The residue was dissolved in ethyl acetate, treated with ethereal hydrogen chloride and the resulting solid was recrystallised from ethanol to give the **title compound** as white needles, (0.626g), m.p. 175 -176°C.
Found: C, 69.42; H, 8.11; N, 4.01; Cl^-, 9.68%

($C_{21}H_{29}NO_2$.HCl) requires: C, 69.31; H, 8.31; N, 3.85; Cl^-, 9.74%

Example 3

N-[7-(4-Benzyloxyphenoxy)heptyl]dimethylamine hydrochloride

The title compound was prepared in a similar manner to Example 2 starting from 7-(4-benzyloxyphenoxy)-1-bromoheptane (1.25g), 33% dimethylamine in ethanol (10ml) and chloroform (50ml). Treatment with ethereal hydrogen chloride and recrystallisation from acetonitrile gave the **title compound** as a white solid, (0.638g), m.p. 152 - 153°C.
Found: C, 68.23; H, 8.37; N, 3.71; Cl, 9.24%
($C_{22}H_{31}NO_2$.HCl.0.5H_2O) requires: C, 68.28; H, 8.59; N, 3.62; Cl, 9.16%

Example 4

N-[7-(4-Benzyloxyphenoxy)heptyl]-N-methyl-N',N'-dimethylethylenediamine dihydrochloride

The title compound was prepared in a similar manner to Example 2 starting from 7-(4-benzyloxyphenoxy)-1-bromoheptane (1.25g), N,N,N'-trimethylethylenediamine (0.37g) and chloroform (100ml). Treatment with ethereal hydrogen chloride and recrystallisation from ethyl acetate gave the **title compound** as a white solid, (0.55g), m.p. 242 - 244°C.
Found: C, 61.78; H, 7.99; N, 5.75%
($C_{25}H_{38}N_2O_2$.2HCl.0.8H_2O) requires: C, 61.71; H, 8.40; N, 5.75%

Example 5

N-[7-(4-Benzyloxyphenoxy)heptyl]-N-butylmethylamine oxalate

A mixture of 7-(4-benzyloxyphenoxy)-1-bromoheptane (1.0g), N-butylmethylamine (0.25g), potassium carbonate (2g) and ethanol (25ml) was stirred at reflux for 18 hours. The mixture was filtered and the residue was washed with ethanol. The filtrates were combined, the solvent removed and the residue partitioned between ether and dilute sodium hydroxide solution. The ether layer was separated, dried over magnesium sulphate and the solvent removed. Chromatography on silica gel eluted with methanol/dichloromethane and treatment with oxalic acid gave a white solid which was recrystallised from ethyl acetate to give the **title compound**,. (0.25g), m.p. 141 - 143°C.
Found: C, 67.79; H, 8.07; N, 3.08%
($C_{25}H_{37}NO_2.C_2H_2O_4$.O.25$H_2O$) requires: C, 67.76; H, 8.15; N, 2.92%

Example 6

N-[7-(4-Benzyloxyphenoxy)heptyl]morpholine hydrochloride

The title compound was prepared in a similar manner to Example 5 starting from 7-(4-benzyloxyphenoxy)-1-bromoheptane (1.5g), morpholine (3.0g), potassium carbonate (3g) and ethanol (50ml). Chromatography on silica gel eluted with methanol/dichloromethane and treatment with ethereal hydrogen chloride gave a white solid which was recrystallised from ethyl acetate to provide the **title compound.** (0.85g), m.p. 174 - 176°C.
Found: C, 68.38; H, 7.95; N, 3.40; Cl, 8.45%
($C_{24}H_{33}NO_3$.HCl) requires: C, 68.64; H, 8.16; N, 3.33; Cl, 8.44%

Example 7

N-[7-(4-Benzyloxyphenoxy)heptyl]cyclohexylamine hydrochloride

The title compound was prepared in a similar manner to Example 1 starting from 7-(4-benzyloxyphenoxy)-1-bromoheptane (1.88g), 80% sodium hydride (0.17g), cyclohexylamine (0.572ml) and dimethylformamide (10ml). Treatment with ethereal hydrogen chloride and recrystallisation from n-propanol followed by further recrystallisation from ethanol gave the **title compound** as a white solid, (0.505g), m.p. 155 - 156°C.
Found: C, 72.14; H, 8.65; N, 3.45 ; Cl, 8.41%
($C_{26}H_{37}NO_2$.HCl) requires: C, 72.28; H, 8.87; N, 3.24; Cl, 8.21%

Example 8

1-[7-(4-Benzyloxyphenoxy)heptyl]-4-methylpiperazine dihydrochloride

The title compound was prepared in a similar manner to Example 1 starting from 7-(4-benzyloxyphenoxy)-1-bromoheptane (1.88g), 80% sodium hydride (0.17g), N-methylpiperazine (0.55ml) and dimethylformamide (10ml). Treatment with ethereal hydrogen chloride and recrystallisation from ethanol gave the **title compound** as a white solid, (0.93g), m.p. 238 - 241°C.
Found: C, 62.83; H, 7.81; N, 5.98; Cl, 14.80%
($C_{25}H_{36}N_2O_2$.2HCl.0.5H_2O) requires: C, 62.75; H, 8.21; N, 5.85; Cl, 14.82%

Example 9

1-[7-(4-Benzoylphenoxy)heptyl]piperidine hydrochloride

A solution of 7-piperidinoheptanol (2.0g), 4-hydroxybenzophenone (1.98g), triphenylphosphine (2.62g) in tetrahydrofuran (100ml) was treated with diethyl azodicarboxylate (1.74g). The resulting solution was stirred at room temperature for 18

hours, the solvent removed and the residue chromatographed on silica gel eluted with methanol/dichloromethane. The resulting oil was dissolved in ethyl acetate and treated with ethereal hydrogen chloride. The precipitate was collected by filtration and recrystallised from acetonitrile to give the **title compound** (2.51g) as white needles, m.p. 178 -180°C.

Found: C, 72.36; H, 7.96; N, 3.59; Cl, 8.51%.

($C_{25}H_{33}NO_2$.HCl) requires: C, 72.18; H, 8.23; N, 3.37; Cl, 8.52%

Example 10

1-[7-(3-Benzoylphenoxy)heptyl]piperidine hydrochloride

A solution of 7-piperidinoheptanol (2.0g), 3-hydroxybenzophenone (1.98g), triphenylphosphine (2.62g) in tetrahydrofuran (100ml) was treated with diethyl azodicarboxylate (1.74g). The resulting solution was stirred at room temperature for 18 hours, the solvent removed and the residue chromatographed on silica gel eluted with methanol/dichloromethane. The resulting oil was dissolved in ethyl acetate and treated with ethereal hydrogen chloride. The precipitate was collected by filtration and recrystallised from acetonitrile to give the **title compound** (1.99g) as white needles, m.p. 88 - 90°C.

Found: C, 72.05; H, 7.89; N, 3.45; Cl, 8.54%.

($C_{25}H_{33}NO_2$.HCl) requires: C, 72.18; H, 8.23; N, 3.37; Cl, 8.52%

Example 11

1-{7-[4-(4-Fluorobenzoyl)phenoxy]heptyl}piperidine hydrochloride

A mixture of 7-piperidinoheptanol (1.0g), 80% sodium hydride in oil (0.15g) and dimethylsulphoxide (25ml) was stirred at 40°C under an atmosphere of argon for 2 hours. The mixture was allowed to cool to room temperature, treated with 4,4'-difluorobenzophenone (2.18g) and stirred for 18 hours. The solvent was removed and the residue treated with water and extracted with ether. The ether layer was washed with water and brine, dried over sodium sulphate and the solvent was removed. Chromatography on silica gel eluted with 10% methanol in chloroform followed by treatment with ethereal hydrogen chloride and recrystallisation from acetonitrile gave the **title compound** as cream coloured needles, (0.946g), m.p. 166 - 167°C.

Found: C, 68.87; H, 7.41; N, 3.46 ; Cl, 8.05%

($C_{25}H_{32}FNO_2$.HCl) requires: C, 69.18; H, 7.66; N, 3.22; Cl, 8.17%

Example 12

1-{7-[4-(1-Methyl-1-phenylethyl)phenoxy]heptyl}piperidine hydrochloride

A solution of 7-piperidinoheptanol (1.0g), 4-cumylphenol (1.07g), triphenylphosphine (1.31g) in tetrahydrofuran (20ml) was treated with diethyl azodicarboxylate (0.87g). The resulting solution was stirred at room temperature for 18 hours, the solvent removed and the residue chromatographed on silica gel eluted with 10% methanol in chloroform. The resulting oil was dissolved in ethyl acetate and treated with ethereal hydrogen chloride. The precipitate was collected by filtration and recrystallised from ethyl acetate to give the **title compound** (1.11g) as a white solid, m.p. 122 -124°C.

Found: C, 75.03; H, 9.16; N, 3.47; Cl, 8.21%.

($C_{27}H_{39}NO.HCl$) requires: C, 75.41; H, 9.37; N, 3.26; Cl, 8.24%

Example 13

1-{7-[4-(4-Chlorobenzoyl)phenoxy]heptyl}piperidine hydrochloride

A solution of 7-piperidinoheptanol (1.0g), 4-chloro-4'-hydroxybenzophenone (1.16g), triphenylphosphine (1.31g) in tetrahydrofuran (20ml) was treated with diethyl azodicarboxylate (0.87g). The resulting solution was stirred at room temperature for 18 hours, the solvent removed and the residue chromatographed on silica gel eluted with 10% methanol in chloroform. The resulting oil was dissolved in ethyl acetate and treated with ethereal hydrogen chloride. The precipitate was collected by filtration and recrystallised from acetonitrile to give the **title compound** (1.13g) as white needles, m.p. 194 -195°C.

Found: C, 66.20; H, 7.09; N, 3.44; Cl^-, 7.82%.

($C_{25}H_{32}ClNO_2.HCl$) requires: C, 66.66; H, 7.38; N, 3.11; Cl^-, 7.82%

Example 14

(±)-1-{7-[4-(1-Phenylethyloxy]phenoxy]heptyl}piperidine hydrochloride

A solution of 7-(4-hydroxyphenoxy)-1-piperidinoheptane (WO93/22302; 0.75g), (±)-1-phenylethanol (0.31g), triphenylphosphine (0.61g) in tetrahydrofuran (20ml) was treated with diethyl azodicarboxylate (0.44g). The resulting solution was stirred at room temperature for 18 hours, the solvent removed and the residue chromatographed on silica gel eluted with 10% methanol in chloroform. The resulting oil was dissolved in ethyl acetate and treated with ethereal hydrogen chloride. The precipitate was collected by filtration and recrystallised from isopropyl acetate to give the **title compound** (0.303g) as a white solid, m.p. 101 - 103°C.

Found: C, 72.14; H, 8.67; N, 3.42; Cl, 8.21%.

($C_{26}H_{37}NO_2.HCl$) requires: C, 72.28; H, 8.87; N, 3.24; Cl, 8.20%

Example 15

6-[4-(4-Fluorophenoxy)phenyl]-6-oxo-1-piperidinylhexane hydrochloride

A solution of 1-bromo-6-[4-(4-fluorophenoxy)phenyl]-6-oxyhexane (2.0g) in dichloromethane (100ml) was treated with piperidine (3.0ml). The solution was allowed to stand at room temperature for 18 hours, washed with dilute sodium hydroxide solution and brine, dried over sodium sulphate and the solvent was removed. The resulting oil was dissolved in ethyl acetate and treated with ethereal hydrogen chloride and the solvent was removed. The residue was chromatographed on silica gel eluted with 10% methanol in dichloromethane and crystallised by trituration with ether to give the **title compound** as an off-white solid, (1.378g), m.p. 151 - 152°C.
Found: C, 67.44; H, 7.01; N, 3.61%
($C_{23}H_{28}FNO_2$.HCl.0.25H_2O) requires: C, 67.30; H, 7.24; N, 3.41%

Example 16

8-[4-(4-Fluorophenoxy)phenyl]-8-oxo-1-piperidinyloctane hydrochloride

The title compound was prepared in a similar manner to Example 15 starting from 1-bromo-8-[4-(4-fluorophenoxy)phenyl]-8-oxyoctane (2.0g) and using corresponding molar amounts of the other reagents. Treatment with ethereal hydrogen chloride and crystallisation under ether gave the **title compound** as a white solid, (1.53g), m.p. 111 - 112°C.
Found: C, 67.95; H, 7.43; N, 3.52%
($C_{25}H_{32}FNO_2$.HCl.0.3H_2O) requires: C, 68.24; H, 7.69; N, 3.18%

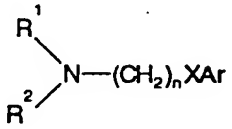
Example 17

6-(4-Phenoxy)phenyl-6-oxo-1-piperidinylhexane hydrochloride

The title compound was prepared in a similar manner to Example 15 starting from 1-bromo-6-(4-phenoxy)phenyl-6-oxyhexane (1.5g) and using corresponding molar amounts of the other reagents. Treatment with ethereal hydrogen chloride and crystallisation under ether gave the **title compound** as a white solid, (1.35g), m.p. 87 - 89°C.

Claims

1. The use of a compound of formula (I):



Formula (I)

wherein

R^1 and R^2 each independently represent:

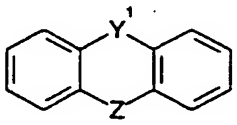
hydrogen, C_{1-8}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-4}alkyl, arylC_{1-4}alkyl, C_{2-6}hydroxyalkyl or $R^3R^4NC_{2-6}$alkyl (where R^3 and R^4 independently represent H or C_{1-4}alkyl) or

NR^1R^2 represents a saturated heterocyclic ring containing 4 to 9 ring members, one of which may optionally be a further heteroatom selected from O, S or NR^5, (where R^5 is H, C_{1-4}alkyl or arylC_{1-4}alkyl), which ring may optionally be substituted by one or two substituents selected from C_{1-6}alkyl and C_{1-6}alkoxy;

X represents O, S, or C=O;

n is 5 to 11; and

Ar represents phenyl optionally substituted by 1-3 substituents selected from halo, C_{1-8}alkyl, C_{1-8}alkoxy, C_{1-2}alkylenedioxy e.g. methylenedioxy, trifluoromethyl, trifluoromethyloxy, or by a group $Ph(Alk^1)_pA(Alk^2)_q$- where Ph is optionally substituted phenyl, A is a bond, O, S, -C=O or CH=CH, Alk^1 and Alk^2 independently represent C_{1-4}alkyl which may be straight or branched and p and q are independently 0 or 1 provided that the length of $-(Alk^1)_pA(Alk^2)_q-$ does not exceed 5 atoms, or Ar is an optionally substituted tricyclic heteroaryl group:



in which Y^1 is $Y^2(CH_2)_r$ where r is 0 or 1 and Y^2 is O, S or NR^6 where R^6 is hydrogen or C_{1-4}alkyl, Z is $(CH_2)_s$ or -CH=CH-, s is 0, 1 or 2 or Ar is the corresponding tricyclic dehydro ring system;

with the provisos that

(i) when X is O or S, and NR^1R^2 represents a heterocyclic ring which does not contain an optional further heteroatom then Ar is phenyl substituted by a group $Ph(Alk^1)_pC(O)(Alk^2)_q$-

(ii) when n is 5 and one of R^1 and R^2 is hydrogen, C_{1-4}alkyl or arylC_{1-4}alkyl, then the other of R^1 and R^2 is not $R^3R^4NC_{2-6}$alkyl;

or a pharmaceutically acceptable salt thereof; in the manufacture of a medicament for the treatment of a condition where a calcium antagonist is required.

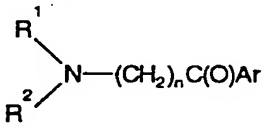
2. Use according to claim 1 wherein the condition is related to the accumulation of calcium in the brain cells of a mammal.

3. Use of a compound according to claim 1 or claim 2 wherein n is from 5 to 9.

4. Use of a compound according to any of claims 1 to 3 wherein X represents oxygen or C=O.

5. Use of a compound according to any of claims 1 to 4 wherein Ar represents phenyl substituted by a group $Ph(Alk^1)_pA(Alk^2)q$-.

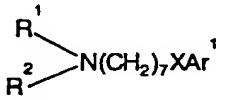
6. A compound of formula (IA):



Formula (IA)

wherein
R^1, R^2, n and Ar are as defined for formula (I); or a salt thereof.

7. A compound of formula (IB) :



Formula (IB)

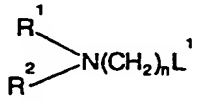
wherein R^1, R^2, and X are as defined for formula (I) and Ar^1 represents phenyl optionally substituted by a group $Ph(Alk^1)_pA(Alk^2)q$- or a tricyclic heteroaryl group as defined for formula (I), provided that when X is O or S, and NR^1R^2 represents a heterocyclic ring which does not contain an optional further heteroatom then Ar^1 is phenyl substituted by a group $Ph(Alk^1)_pC(O)(Alk^2)_q$-,
or a salt thereof.

8. A compound of formula (I) selected from :
N-[7-(4-benzyloxyphenoxy)heptyl]-N-methylcyclohexylamine,

N-[7-(4-benzyloxyphenoxy)heptyl]methylamine,
N-[7-(4-benzyloxyphenoxy)heptyl]dimethylamine,
N-[7-(4-benzyloxyphenoxy)heptyl]-N-methyl-N',N'-dimethylethylenediamine,
N-[7-(4-benzyloxyphenoxy)heptyl]-N-butylmethylamine,
N-[7-(4-benzyloxyphenoxy)heptyl]morpholine,
N-[7-(4-benzyloxyphenoxy)heptyl]cyclohexylamine,
1-[7-(4-benzyloxyphenoxy)heptyl]-4-methylpiperazine,
1-[7-(4-benzoylphenoxy)heptyl]piperidine,
1-[7-(3-benzoylphenoxy)heptyl]piperidine,
1-{7-[4-(4-fluorobenzoyl)phenoxy]heptyl}piperidine,
N-{7-[4-(4-fluorobenzyl)-phenoxy]heptyl}piperidine,
1-{7-[4-(1-methyl-1-phenylethyl)phenoxy]heptyl}piperidine,
1-{7-[4-(4-chlorobenzoyl)phenoxy]heptyl}piperidine
(±)-1-{7-[4-(1-phenylethyloxy]phenoxy]heptyl}piperidine,
6-[4-(4-fluorophenoxy)phenyl]-6-oxo-1-piperidinylhexane,
8-[4-(4-fluorophenoxy)phenyl]-8-oxo-1-piperidinyloctane,
6-(4-phenoxy)phenyl-6-oxo-1-piperidinylhexane
or a salt thereof.

9. A process for the preparation of a novel compound of formula (I) which comprises:

(a) to prepare a compound wherein X represents O or S reaction of a compound of formula (II):



Formula (II)

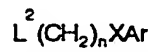
in which R^1, R^2, and n are as defined in formula (I), and L^1 is a group displaceable with a nucleophile with a compound of formula (III) :

HXAr

Formula (III)

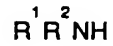
in which Ar and X are as defined in formula (I);

(b) reaction of a compound of formula (IV) :



Formula (IV)

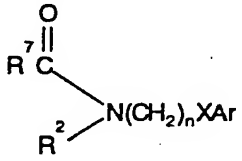
in which Ar, X and n are as defined for formula (I),and L^2 is a leaving group, with a compound of formula (V) :



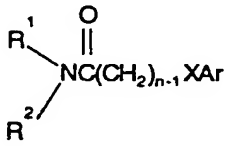
Formula (V)

in which R^1 and R^2 are as defined in formula (I); or

(c) reduction of an amide of formula (VI) or (VII) :



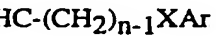
Formula (VI)



Formula (VII)

wherein R^1, R^2, X, Ar and n are as defined above and  is a group reducible to R^1;

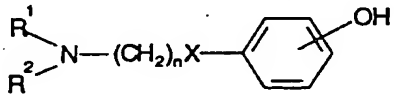
d) Reductive amination of an aldehyde of formula (VIII) :



Formula (VIII)

wherein Ar, X, and n are as hereinbefore defined, in the presence of a compound of formula (V) as defined above.

e) To prepare a compound wherein Ar represents phenyl substituted by $Ph(Alk^1)_pO$-, alkylation of a compound of formula (IX) :



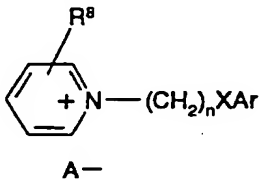
Formula (IX)

wherein R^1, R^2, X, and n are as hereinbefore defined; with an alkylating agent of formula (X) :

Formula (X)

wherein Ph, Alk^1, p and L^1 are as hereinbefore defined.

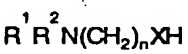
f) To prepare a compound where R^1R^2N- represents an optionally substituted piperidine ring, reduction of a pyridine derivative of formula (XI) :



Formula (XI)

wherein Ar, X, and n are as hereinbefore defined, R^8 represents hydrogen or an optional substituent as hereinbefore defined and A^- is a counter anion;

g) to prepare a compound where X represents O or S, reaction of a compound of formula (XII) :



Formula (XII)

wherein R^1, R^2 and n are as hereinbefore defined and X is O or S,
with a compound F-Ar;

h) Interconversion of one compound of formula (I) to a different compound of formula (I) e.g.

(i) reduction of a compound wherein A represents CH=CH to a compound wherein A represents $-CH_2CH_2-$;

(ii) reduction of a compound wherein A and/or X represent C=O to a compound wherein A and/or X represent $-CH_2-$;
followed if desired by salt formation.

10. A pharmaceutical composition comprising a novel compound of formula (I) as hereinbefore defined or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

11. A method of treatment of a condition or disease related to the accumulation of calcium in the brain cells of a mammal which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) as defined in any of claims 1 or 3 to 8 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 94/03425

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D295/088 A61K31/435 C07C217/54 A61K31/495 A61K31/525

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 382 629 (SANOFI) 16 August 1990 see page 18, line 23 - line 24; claim 1	1-5,7
P,Y	WO,A,93 22302 (SMITHKLINE BEECHAM CORPORATION) 11 November 1993 see claim 1	1-5,7
Y	EP,A,0 302 792 (SANOFI) 8 February 1989 see claim 1	1-5,7
Y	GB,A,2 113 680 (DELALANDE) 10 August 1983 see claim 1	1-5,7
A	EP,A,0 103 252 (BASF AG) 21 March 1984 cited in the application see claim 1	7

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 February 1995	06. 03. 95
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Gettins, M

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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PC1/EP 94/03425

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR,A,1 601 591 (ARIES) 31 August 1970 cited in the application see claim 1	7
A	GB,A,924 961 (WELLCOME) 1 May 1963 cited in the application see claim 1	7

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INTERNATIONAL SEARCH REPORT

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Inte onal Application No
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